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EXAMINER	
GUSSOW, ANNE	

ART UNIT	PAPER NUMBER
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/572,740	HOFMEISTER ET AL.	
	Examiner	Art Unit	
	Anne M. Gussow	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 November 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35 and 37-41* is/are pending in the application.

4a) Of the above claim(s) *20,22,24 and 26-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19,21,23,25,32-35 and 37-41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 March 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/21/06, 7/13/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Sequence alignments*.

DETAILED ACTION

1. Applicant's election with traverse of Group I, claims 1-26, 32, 33 in part, 34, 35, 37-40, and 41 in part, and the species of SEQ ID Nos. 88, 92, 96, 100, 102, and 104, in the reply filed on November 20, 2009 is acknowledged. The traversal is on the ground(s) that there would not be a search burden to examine both the amino acids and the nucleic acids. This is not found persuasive because a search of amino acids requires the search of 5-10 amino acid databases and a search of a nucleotide sequence requires the search of 5-10 different nucleotide databases which are not encompassed by the amino acid databases. Therefore there would be a search burden to examine all groups.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 27-31 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on November 20, 2009.

3. Claims 20, 22, 24, and 26 withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on November 20, 2009.

4. Claims 1-19, 21, 23, 25, 32-35, and 37-41 are under examination.

Priority

5. Applicant is advised of possible benefits under 35 U.S.C. 119(a)-(d), wherein an application for patent filed in the United States may be entitled to the benefit of the filing date of a prior application filed in a foreign country.

6. Receipt is acknowledged of a certified copy of the European application EP 03023581.6 application filed by the International Bureau If this copy is being filed to obtain the benefits of the foreign filing date under 35 U.S.C. 119(a)-(d), applicant should also file a claim for such priority as required by 35 U.S.C. 119(b). If the application being examined is an original application filed under 35 U.S.C. 111(a) (other than a design application) on or after November 29, 2000, the claim for priority must be presented during the pendency of the application, and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior foreign application. See 37 CFR 1.55(a)(1)(i). If the application being examined has entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the claim for priority must be made during the pendency of the application and within the time limit set forth in the PCT and Regulations of the PCT. See 37 CFR 1.55(a)(1)(ii). Any claim for priority under 35 U.S.C. 119(a)-(d) or (f) or 365(a) or (b) not presented within the time period

set forth in 37 CFR 1.55(a)(1) is considered to have been waived. If a claim for foreign priority is presented after the time period set forth in 37 CFR 1.55(a)(1), the claim may be accepted if the claim properly identifies the prior foreign application and is accompanied by a grantable petition to accept an unintentionally delayed claim for priority. See 37 CFR 1.55(c).

7. For the purposes of this office action, since applicant has not claimed priority to the foreign document the claims receive the filing date of the international application, October 15, 2004, as the priority date for art rejection purposes.

Information Disclosure Statement

8. The information disclosure statements (IDS) submitted on March 21, 2006 and July 13, 2006 have been considered by the examiner and an initialed copy of the IDS is included with the mailing of this office action.

Specification

9. The abstract of the disclosure is objected to because it contains legal phraseology. Correction is required. See MPEP § 608.01(b).

10. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract

on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

11. The disclosure is objected to because of the following informalities: the specification contains sequences on pages 11 and 85 that are not identified by SEQ ID No. and do not appear to be included in the sequence listing. See 37 CFR §1.821-1.825

Appropriate correction is required.

12. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

The browser executable code is on pages 11 and 69 of the specification.

Claim Rejections - 35 USC § 112

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 1-19, 21, 23, 25, 32-35, and 37-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-19, 21, 23, 25, 32-35 and 37-41 are indefinite for reciting "derived" in claims 1, 14-16, 18, 19, 21, 23, and 25 because the exact meaning of the term is not clear. The term "derived" is not one, which has a universally accepted meaning in the art nor is it one which has been adequately defined in the specification. The primary deficiency in the use of this phrase is the absence of an ascertainable meaning for said phrase. Since it is unclear how the Ig domain are to be derivatized from one or more immunoglobulins to yield the class of derivatives referred to in the claims, there is no way for a person of skill in the art to ascribe a discrete and identifiable class of compounds to said phrase. In addition, since the term "derived" does not appear to be clearly defined in the specification, the term can encompass proteins with amino acid substitutions, insertions, or deletions, chemically derivatized molecules, or even mimetics. In the absence of a single defined art recognized meaning for the phrase and lacking a definition of the term "derived" in the specification, one of skill in the art could not determine the metes and bounds of the claims.

15. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

16. Claim 18 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claim is drawn to an antibody construct comprising a second binding domain selected from a large group of antigens.

The specification discloses antibody constructs that bind to CD3 and a second antigen, wherein the second antigen is EpCAM, CCR5, CD19, or CD20. The specification does not provide sufficient written description as to the structural features of the claimed antibody constructs that would bind to other antigens.

A "representative number of species" means that the species, which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. The disclosure of only one species encompassed within a genus adequately describes a claim directed to that genus only if the disclosure "indicates that the patentee has invented species sufficient to constitute the gen[us]." See Enzo Biochem, 323 F.3d at 966, 63 USPQ2d at 1615; Noelle v. Lederman, 355 F.3d 1343, 1350, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) (Fed. Cir. 2004)("[A] patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated."). "A

patentee will not be deemed to have invented species sufficient to constitute the genus by virtue of having disclosed a single species when ... the evidence indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed." In re Curtis, 354 F.3d 1347, 1358, 69 USPQ2d 1274, 1282 (Fed. Cir. 2004)(Claims directed to PTFE dental floss with a friction-enhancing coating were not supported by a disclosure of a microcrystalline wax coating where there was no evidence in the disclosure or anywhere else in the record showing applicant conveyed that any other coating was suitable for a PTFE dental floss.).

It has been well known that minor structural differences even among structurally related compounds can result in substantially different biology, expression and activities. Based on the instant disclosure one of skill in the art would not know which sequences of the antibody are essential and which are non-essential and what particular sequence lengths of which antigenic proteins identify essential sequences for identifying an epitope encompassed by the claimed binding specificity. For example, there is insufficient guidance based on the reliance of disclosure of the antibody clones CD3-EpCAM, CD3-CCR5, CD3-CD19, or CD3-CD20 to identify the specific sites necessary to bind just any antigen. Mere idea of function is insufficient for written description; isolation and characterization at a minimum are required.

The state of the prior art is such that the formation of an intact antigen-binding site of antibodies routinely requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs or hypervariable regions, which provide the majority of the contact residues for the binding

of the antibody to its target epitope (Paul, Fundamental Immunology, 3rd Edition, 1993, pp. 292-295, under the heading "Fv Structure and Diversity in Three Dimensions"). The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity, which is characteristic of the immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites (Paul, page 293, first column, lines 3-8 and line 31 to column 2, line 9 and lines 27-30). Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff, et al. (Proceedings of the National Academy of Sciences, 1982. Vol. 79, pages 1979-1983). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. Colman (Research in Immunology, 1994. Vol. 145, pages 33-36) teaches that even a very conservative substitution may abolish binding or may have very little effect on the binding affinity (see pg. 35, top of left column and pg. 33, right column). While there are some publications, which acknowledge that CDR3 is important, the conformations of other CDRs as well as framework residues influence binding. MacCallum, et al. (Journal of Molecular Biology, 1996. Vol. 262, pages 732-745) analyzed many different antibodies for interactions with antigen and state that although

CDR3 of the heavy and light chain dominate, a number of residues outside the standard CDR definitions make antigen contacts (see page 733, right column) and non-contacting residues within the CDRs coincide with residues as important in defining canonical backbone conformations (see page 735, left column). Thus, the art discloses that a change of even one amino acid of an antibody may change the ability of that antibody to bind to its original epitope. In addition, the art discloses that amino acids outside the CDRs are critical for antigen binding.

In the absence of sufficient guidance and direction to the structural and functional analysis, applicant's reliance on the antibody clones CD3-EpCAM, CD3-CCR5, CD3-CD19, or CD3-CD20 disclosed in the specification as-filed does not appear to provide sufficient written description for the genus of antibodies binding a specific epitope in view of the above evidence, which indicates ordinary artisans could not predict the operability in the invention of any species other than the one disclosed.

For inventions in an unpredictable art, adequate written description of a genus, which embraces widely variant species cannot be achieved by disclosing only one species within the genus. In the instant case, applicant has not even disclosed a single species encompassed by the highly variant genus nor is there disclosure of the common attributes or features (i.e., structural domains) that are essential for activity or those which are non-essential. See, e.g., Eli Lilly. Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces. If a representative number of adequately described species are not disclosed for a genus, the claim to that

genus must be rejected as lacking adequate written description under 35 U.S.C. 112, first paragraph.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). As discussed above, the skilled artisan cannot envision the detailed structure of the encompassed genus of antibodies binding an undisclosed epitope, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See Fiefs v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddles v.Baird, 30 USPQ2d 1481, 1483. In Fiddles v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Therefore, only isolated antibody clones CD3-EpCAM, CD3-CCR5, CD3-CD19, or CD3-CD20, comprising all 6 CDR regions, but not the full breadth of the claim meets

the written description provision of 35 U.S.C. § 112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115).

17. Claims 1-19, 21, 23, 25, 32-35, and 37-41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody construct comprising three heavy chain CDR regions and three light chain CDR regions, does not reasonably provide enablement for an antibody construct comprising fewer than all 6 CDR regions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CA FC 1988).

> Wands states on page 1404,
> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims are broadly drawn to an antibody comprising a single defined CDR, CDR-H3. Although the claim language recites a CDR-H1, CDR-H2, and CDR-H3, applicant has defined a single CDR, CDR-H3, by SEQ ID No. When defining an

antibody by CDR sequence it is necessary to define all six CDR sequences for the reasons set forth below.

The specification discloses antibody constructs containing three heavy chain CDRs and three light chain CDRs. The specification does not disclose antibodies that bind to antigen and comprise fewer than all six CDR regions.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff, et al. (Proceedings of the National Academy of Sciences, 1982. Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function.

MacCallum, et al. (Journal of Molecular Biology, 1996. Vol. 262, pages 732-745) analyzed many different antibodies for interactions with antigen and state that although CDR3 of the heavy and light chain dominate, a number of residues outside the standard CDR definitions make antigen contacts (see page 733, right column) and non-contacting residues within the CDRs coincide with residues as important in defining canonical backbone conformations (see page 735, left column). De Pascalis, et al. (Journal of Immunology, 2002. Vol. 169, pages 3076-3084) demonstrate that grafting of the CDRs into a human framework was performed by grafting CDR residues and maintaining framework residues that were deemed essential for preserving the structural integrity of the antigen binding site (see page 3079, right column). Although abbreviated CDR residues were used in the constructs, some residues in all 6 CDRs were used for the constructs (see page 3080, left column).

The fact that not just one CDR is essential for antigen binding or maintaining the conformation of the antigen binding site is underscored by Casset, et al. (Biochemical and Biophysical Research Communications, 2003. Vol. 307, pages 198-205) which constructed a peptide mimetic of an anti-CD4 monoclonal antibody binding site by rational design and the peptide was designed with 27 residues formed by residues from 5 CDRs (see entire document). Casset, et al. also states that although CDR H3 is at the center of most if not all antigen interactions, clearly other CDRs play an important role in the recognition process (page 199, left column) and this is demonstrated in this work by using all CDRs except L2 and additionally using a framework residue located just before the H3 (see page 202, left column). Vajdos, et al. (Journal of Molecular

Biology, 2002. Vol. 320, pages 415-428) additionally state that antigen binding is primarily mediated by the CDRs more highly conserved framework segments which connect the CDRs are mainly involved in supporting the CDR loop conformations and in some cases framework residues also contact antigen (page 416, left column). Holm, et al. (Molecular Immunology, 2007. Vol. 44, pages 1075-1084) describes the mapping of an anti-cytokeratin antibody where although residues in the CDR3 of the heavy chain were involved in antigen binding unexpectedly a residue in CDR2 of the light chain was also involved (abstract). Chen, et al. (Journal of Molecular Biology, 1999. Vol. 293, pages 865-881) describe high affinity variant antibodies binding to VEGF wherein the results show that the antigen binding site is almost entirely composed of residues from heavy chain CDRs, CDR-H1, H2, H3 (page 866). Wu, et al. (Journal of Molecular Biology, 1999. Vol. 294, pages 151-162) state that it is difficult to predict which framework residues serve a critical role in maintaining affinity and specificity due in part to the large conformational change in antibodies that accompany antigen binding (page 152 left column) but certain residues have been identified as important for maintaining conformation.

There is insufficient evidence or nexus that would lead the skilled artisan to predict the ability to produce a functional antibody comprising fewer than 6 CDR regions. The specification does not teach how to make an antibody that would bind CD3 and comprise fewer than 6 CDR regions.

In view of the lack of the predictability of the art to which the invention pertains, undue experimentation would be required to make the claimed antibody with a

reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively produce the claimed antibody and absent working examples providing evidence which is reasonably predictive that the claimed antibodies are effective binding molecules, commensurate in scope with the claimed invention.

18. Claims 37-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inducing cytotoxicity in a cell expressing CD3, does not reasonably provide enablement for a method of preventing just any disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CA FC 1988).

> Wands states on page 1404,
> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims are broadly drawn to the method of preventing or treating any disease or disorder by administering an antibody construct.

The specification discloses cytotoxic activity in cell lines by administering the antibody constructs. The specification does not disclose administration of the antibodies to treat or prevent any disease.

Reasonable guidance with respect to preventing any disease relies on quantitative analysis from defined populations which have been successfully pre-screened and are predisposed to particular types of disease or have had such disease. The essential element towards the validation of a preventive therapeutic is the ability to test the drug on subjects monitored in advance of clinical disease and link those results with subsequent histological confirmation of the presence or absence of disease. This irrefutable link between antecedent drug and subsequent knowledge of the prevention of the disease is the essence of a valid preventive agent. Further, a preventive administration also must assume that the therapeutic will be safe and tolerable for anyone susceptible to the disease. All of this underscores the criticality of providing workable examples which are not disclosed in the specification.

Furthermore, with regards to the prevention of disease comprising administering an antibody, the specification does not disclose sufficient guidance or objective evidence that such antibodies would predictably prevent the formation of disease. The majority of studies suggest that the essential element towards the validation of a preventive therapeutic is the ability to test the drug on subjects monitored in *advance* of clinical disease and *link* those results with subsequent histological confirmation of the presence or absence of disease. Further, such studies require the appropriate experimental models for analyzing chemo- or immunoprevention. For example,

Granziero, et al. (European Journal of Immunology, 1999. Vol. 29 pages 1127-1138) teach that many models are not suitable for testing immunotherapeutic approaches intended to cure cancer. They suggest that the optimal model (breast, pancreatic, or lung cancer, in their case) would have spontaneous tumor development in its natural location (1st column, page 1128) wherein disease progression would closely resemble the progression of the particular type of cancer. Hence, depending on the type of model employed one could establish a reasonable link between antecedent drug and subsequent knowledge of the prevention of the disease. Byers (CA Cancer Journal, 1999. Vol. 49, pages 353-361) teaches that randomized controlled trials are commonly regarded as the definitive study for proving causality (1st col., p.358), and that in controlled trials the random assignment of subjects to the intervention eliminates the problems of dietary recalls and controls the effects of both known and unknown confounding factors. Further, Byers suggests that chemo-preventative trials be designed "long-term" such that testing occurs over many years (2nd col., p. 359). The specification is devoid of any models or experimental analysis that reasonably suggests that the claimed method would predictably prevent the formation of disease. This, combined with the state of the art of preventing disease, suggests that undue experimentation would be required to practice the invention as broadly claimed. Given the above and given the absence of evidence in an in vitro or in vivo model drawn to the treatment or prophylaxis of a disease by administering an antibody, one of skill in the art would not believe it more likely than not that one of skill in the art could practice the claimed invention without undue experimentation.

Claim Rejections - 35 USC § 101

19. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

20. Claims 1-13, 15, 16, and 33 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 1-13, 15, 16, and 33, as written, do not sufficiently distinguish over antibodies as they exist naturally because claims 1-13, 15, 16, and 33 do not particularly point out any non-naturally occurring differences between the claimed antibodies and the structure of naturally occurring antibodies. The claims read on naturally occurring antibodies because the second binding domain as claimed could be an Fc binding region of the constant domain of an antibody since it is not clear how the Ig-derived domain is derived, as set forth above.

In the absence of the hand of man, the naturally occurring antibodies are considered non-statutory subject matter (Diamond v. Chakrabarty, 206 U.S.P.Q. 193 (1980)). It should be noted that the mere purity of a naturally occurring product does not necessarily impart patentability (Ex parte Siddiqui, 156 U.S.P.Q. 426 (1966)). However, when purification results in a new utility, patentability is considered (Merck Co. v. Chase Chemical Co., 273 F.Supp 68 (1967), 155 USPQ 139, (District Court, New Jersey, 1967)). Amendment of the claims to recite "an isolated" or "purified" antibody or similar language would obviate this rejection.

Claim Rejections - 35 USC § 103

21. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

22. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

23. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

24. Claims 1, 3, 5, 15-17, 32, 33-35 and 37-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bendig, et al. (WO 92/15683, published September 17, 1992) in view of Joliffe, et al. (US PAT 5,929,212, issued July 27, 1999).

The claims recite a cytotoxically active CD3 specific binding construct comprising a first domain specifically binding to human CD3 and an Ig-derived second binding domain, wherein said first domain is deimmunized and comprises a CDR-H1 region, a CDR-H2 region and a CDR-H3 region, said CDR-H3 region comprising an amino acid sequence as depicted in SEQ ID NO.: 96; and wherein said first domain further comprises in its framework H1 the sequence VKK and wherein the transition sequence between framework H1 and CDRH1 region comprises the sequence Ala-Ser-Gly-Tyr-Thr-Phe (ASGYTF; SEQ ID NO.: 233), further comprising in said first domain a framework H3 comprising the sequence Ile-Thr-Thr-Asp-Lys (ITTDK; SEQ ID NO.: 235), wherein said first domain which specifically binds to human CD3 comprises a framework H2 as shown in SEQ ID NO.: 156 or 157, wherein said Ig-derived second domain and/or (a) connecting linker-region(s) is/are humanized and/or deimmunized, wherein said Ig-derived second domain comprises an antigen-interaction-site with specificity for a cell surface molecule, wherein said cell surface molecule is a tumor specific marker. A process for the production of a CD3 specific binding construct of claim 1, said process comprising culturing a host transformed or transfected with a vector comprising a nucleic acid sequence encoding a CD3 specific construct of claim 1 under conditions allowing the expression of the polypeptide construct and recovering the produced polypeptide construct from the culture. A composition comprising a CD3

specific binding construct of claim 1 and, optionally, a proteinaceous compound capable of providing an activation signal for immune effector cells, which is a pharmaceutical composition further comprising, optionally, suitable formulations of carrier, stabilizers and/or excipients, which is a diagnostic composition further comprising, optionally, means and methods for detection. A method for the prevention, treatment or amelioration of a proliferative disease, a tumorous disease, an inflammatory disease, an immunological disorder, an autoimmune disease, an infectious disease, viral disease, allergic reactions, parasitic reactions, graft-versus-host diseases or host-versus-graft diseases comprising the administration of a CD3 specific binding construct of claim 1 to a subject in need of such a prevention, treatment or amelioration, wherein said subject is a human, further comprising, the administration of a proteinaceous compound capable of providing an activation signal for immune effector cells, wherein said proteinaceous compound is administered simultaneously or non-simultaneously with the CD3 specific binding construct.

Bendig, et al. teach humanization of antibody molecules comprising a peptide that is identical to the instant SEQ ID No. 233 (see sequence alignment). Bendig, et al. teach the antibody molecules for the treatment and diagnosis of tumors. Bendig, et al. do not teach an antibody that binds to CD3. This deficiency is made up for in the teachings of Joliffe, et al.

Joliffe, et al. teach production humanized recombinant antibody molecules that bind to CD3 and comprise a sequence that is identical to the instant SEQ ID Nos. 96, 88, 235, 156, and 157 (see sequence alignment). Joliffe, et al. teach the antibodies in a

pharmaceutical composition with an acceptable carrier for diagnostic purposes or for treatment of acute allograft rejection.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a recombinant antibody comprising the sequence of Bendig, et al. and the sequences of Joliffe, et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a recombinant antibody comprising the sequence of Bendig, et al. and the sequences of Joliffe, et al. because Joliffe, et al. teach humanization of rodent antibodies to reduce the immunogenicity of the antibody in administration to humans. Additionally, Bendig, et al. teach the importance of humanizing murine antibodies to reduce a HAMA response. Further, one of ordinary skill in the art would recognize in humanizing antibodies that the CDRs are the essential components for binding and would thus mutate the framework regions to reduce immunogenicity of the antibodies. Thus, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a recombinant antibody comprising the sequence of Bendig, et al. and the sequences of Joliffe, et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

25. Claims 1-3, 5, 15-18, 32-35, and 37-40 are rejected under 35 U.S.C. 103(a) as being obvious over Joliffe, et al. (US PAT 5,929,212, issued July 27, 1999) in view of Carr, et al. (WO 2002/069232, published September 6, 2002, as cited on the IDS).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Claims 1, 3, 5, 15-17, 32, 33-35 and 37-40 have been described supra. Claims 2 and 18 recite the cytotoxically active CD3 specific binding construct of claim 1 further comprising in said first domain a framework H3 comprising the sequence Met-Glu-Leu-Ser (MELS; SEQ ID NO.: 234). The CD3 specific binding construct of claim 16, wherein said Ig-derived second binding domain comprises an antigen- interaction site with a

specificity for a molecule selected from the group consisting of EpCAM, CCR5, CD19, HER-2, HER-2 neu, HER-3, HER-4, EGFR, PSMA, CEA,, MUC-1 (mucin), MUC2, MUC3, MUC4, MUC5Ac, MUC5B, MUC7, βhCG, Lewis-Y, CD20, CD33, CD30, ganglioside GD3, 9-O-Acetyl-GD3, GM2, Globo H, fucosyl GM1, Poly SA, GD2, Carboanhydrase IX (MN/CA IX), CD44v6, Sonic Hedgehog (Shh), Wue-1, Plasma Cell Antigen, (membrane-bound) IgE, Melanoma Chondroitin Sulfate Proteoglycan (MCSP), CCR8, TNF-alpha precursor, STEAP, mesothelin, A33 Antigen, Prostate Stem Cell Antigen (PSCA), Ly-6; desmoglein 4, E-cadherin neo-epitope, Fetal Acetylcholine Receptor, CD25, CA19-9 marker, CA-125 marker and Muellerian Inhibitory Substance (MIS) Receptor type II, sTn (sialylated Tn antigen, TAG72), FAP (fibroblast activation antigen), endosialin, EGFRvIII, L6, SAS, CD63, TAG72, TF-antigen, Cora antigen, CD7, CD22, Igα, Igβ, G250, gp100, MT-MMPs, F19-antigen, CO-29 and EphA2.

Joliffe, et al. has been described supra. Joliffe, et al. do not teach an antibody that comprises SEQ ID Nos. 233 or 234. This deficiency is made up for in the teachings of Carr, et al.

Carr, et al. teach production of antibodies with reduced immunogenicity that bind to a number of antigens including GD2, Her2, and CD20.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a recombinant antibody comprising the sequences of Joliffe, et al. and the framework sequences of Carr, et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a recombinant antibody

comprising the sequences of Joliffe, et al. and the framework sequences of Carr, et al. because Joliffe, et al. teach humanization of rodent antibodies to reduce the immunogenicity of the antibody in administration to humans. Additionally, Carr, et al. teach modification of existing antibodies to reduce immunogenicity for therapeutic purposes in humans. Further, one of ordinary skill in the art would recognize in humanizing antibodies that the CDRs are the essential components for binding and would thus mutate the framework regions to reduce immunogenicity of the antibodies. Thus, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a recombinant antibody comprising the sequences of Joliffe, et al. and the framework sequences of Carr, et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

26. No claims are allowed.

27. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

a. Lindhofer, et al. (US PG PUB 2002/0009430, published January 24, 2002).

b. Kufer, et al. (US PAT 7,235,641, filed December 22, 2003)

c. Kufer, et al. (US PAT 7,635,742, PCT filed May 26, 2004, priority to May 31, 2003)

28. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne M. Gussow whose telephone number is (571)272-6047. The examiner can normally be reached on Monday - Friday 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anne M. Gussow
February 12, 2010

/Anne M. Gussow/
Examiner, Art Unit 1643